RSC Advances

COMMUNICATION

View Article Online
View Journal | View Issue

First total synthesis of cryptosporiopsin A†

Barla Thirupathi and Debendra K. Mohapatra*

Cite this: *RSC Adv.*, 2014, **4**, 8027

Received 5th December 2013
Accepted 10th January 2014

DOI: 10.1039/c3ra47341d

www.rsc.org/advances

The first total synthesis of polyketide natural product cryptosporiopsin A (1) was described. It has been accomplished in 12 longest linear steps with 15.4% overall yield starting from enantiomerically pure epoxide 12 prepared by hydrolytic kinetic resolution. Other key steps were Stille coupling, Grignard reaction, De Brabander's esterification and ring closing metathesis (RCM) reaction.

One of the most promising groups of natural products that have recently emerged as new lead structures for kinase inhibition is the resorcylic acid lactones (RALs), a unique class of fungal polyketide metabolites, which are β-resorcylic acid derivatives possessing a C11 side that is closed to form a 14-membered macrolactone ring (Fig. 1).[1] Since the first isolation of radicicol (monorden) in 1953,[2] followed by zearalenone in 1962,[3] LL-Z1640-2 in 1978,[4] and hypothemycin in 1980 (ref. 5) more than 30 naturally RALs have been reported. The RALs are endowed with a breadth of biological activity such as transcription factor modulations (zearalenone[6] and zearalenol[7]), HSP90 inhibitors (radicicol[8] and pochonin D[9]), reversible (aigialomycin D[10]) as well as irreversible kinase inhibitors (hypothemycin,[11] IL-Z1640-2,[12] and L-783277 (ref. 13)), antifungal,[14] antimalarial,[15] antiparasitic,[16] cytotoxic,[17] oestrogenic,[18] nematicidal,[19] protein tyrosine kinase and ATPase inhibition activities.[20]

It can thus be safe to be argued that the RAL framework is privileged[21] and that even analogues of these natural products should be of interest. Recently, Laatsch *et al.*[22] reported the isolation of a new resorcylic acid lactone, cryptosporiopsin A (**1**) from *Cryptosporiopsis* sp. an endopyhtic fungus from leaves and branches of *Zanthoxylum leprieurii* (Rutaceae). The relative and absolute configuration of cryptosporiopsin A was assigned on the basis of spectroscopic and spectrometric data. Cryptosporiopsin A (**1**) showed motility inhibitory and lytic activities against zoospores of the grapevine downy mildew pathogen *Plasmopara viticola* as well as potent inhibitory activity against mycelial growth of phytopathogens, *Pythium ultimum*, *Aphanomyces cochlioides* and a basidiomycetous fungus *Rhizoctonia solani*. It also exhibited weak cytotoxic activity against brine shrimp larvae.[22] Because of its promising biological activities and scarcity of the target natural product **1**, we became interested in its total synthesis.

Construction of macrolactone through the formation of C–C bond and particularly by intramolecular ring closing metathesis (RCM) reaction stands as a promising tool for the synthesis of macrolides and heterocycles.[23] As part of our ongoing program in exploring ring-closing metathesis for macrolide syntheses,[24] we demonstrated the use of RCM for the total synthesis of

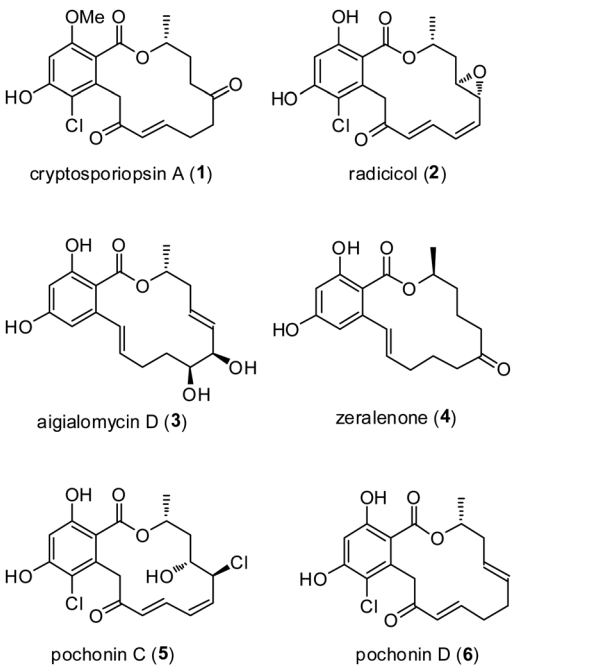


Fig. 1 Structures of some resorcyclic acid lactones (RALs).

Natural Products Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, India. E-mail: mohapatra@iict.res.in; dkm0077@gmail.com

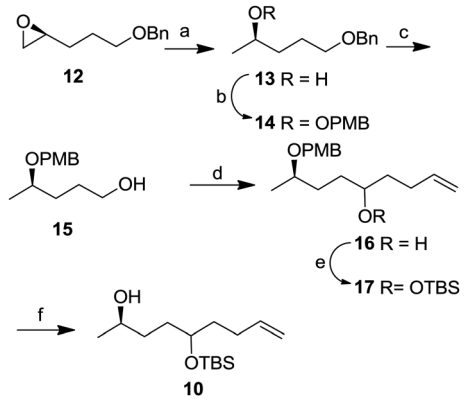
† Electronic supplementary information (ESI) available: Experimental details and scanned copies of ^{1}H and ^{13}C NMR spectra for new compounds. See DOI: 10.1039/c3ra47341d

cryptosporiopsin A. According to our retrosynthetic analysis of cryptosporiopsin A, shown in Scheme 1, could be achieved through RCM reaction of **8** which in turn could be obtained by coupling of lactone **9** and alcohol **10**. Lactone **9** and alcohol **10** could be obtained from 2,4,6-trihydroxy benzoic acid **11** and epoxide **12**, respectively.

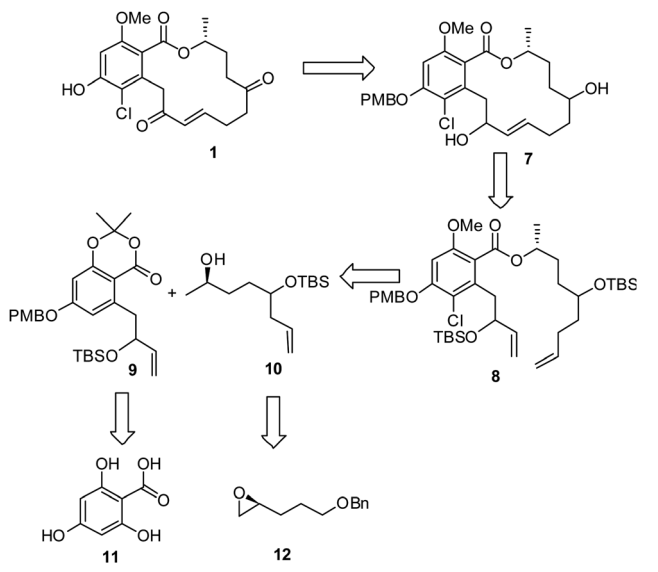
Results and discussion

The synthesis of compound **10** was started from enantiomerically pure epoxide **12** in seven steps (Scheme 2). Epoxide **12** was prepared by Jacobsen's hydrolytic kinetic resolution from racemic epoxide in 45% yield with 99% ee (by HPLC).[25] Treatment of the epoxide with $LiAlH_4$ in THF furnished the corresponding secondary alcohol **13** in 85% yield.[26] The hydroxyl group present in **13** was protected as its PMB ether to obtain **14** in 91% yield. Benzyl ether present in **14** was selectively deprotected[27] by Raney Ni in 88% yield and the resulting primary alcohol was converted to its corresponding aldehyde by using BAIB, TEMPO[28] and subsequently used for the Grignard reaction to get the desired product **16** in (with ≈1 : 1 diastereomers by NMR and HPLC) 72% yield over two steps. The hydroxyl group present in **16** was protected as its TBS ether using TBDMSCl and imidazole in CH_2Cl_2 at room temperature to afford **17** (≈1 : 1 diastereomeric mixture) in 96% yield. PMB group present in **17** was selectively deprotected by careful treatment of DDQ[29] in CH_2Cl_2–H_2O (9 : 1) to produce compound **10** (≈1 : 1 diastereomeric mixture) in 89% yield.

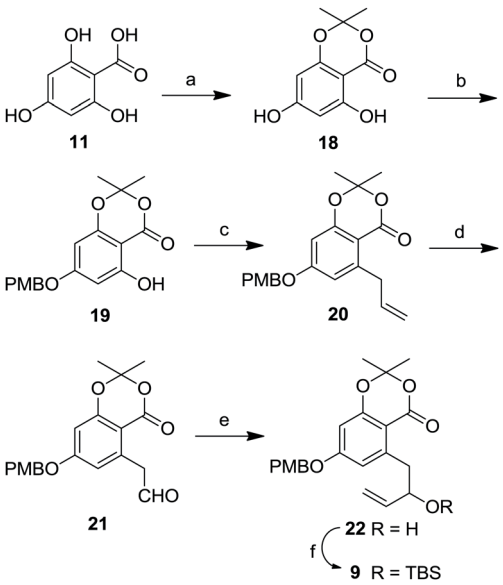
The aromatic coupling fragment was prepared in six steps starting from readily available 2,4,6-trihydroxy benzoic acid monohydrate (**11**) which on treatment with trifluoroacetic acid, trifluoroacetic anhydride and acetone to obtain compound **18** in 55% yield (Scheme 3).[30] The hydroxyl group present in **18** was selectively protected as its PMB ether by using Mitsunobu conditions[31] to afford **19** in 85% yield. Compound **19** was easily converted to its triflate with triflic anhydride in pyridine.[32] Then it was subjected to allylation in presence of catalytic amount $Pd(PPh_3)_4$ in anhydrous DMF to give **20** in 76% yield over two steps.[24c,33] By utilizing Jin's one-step dihydroxylation–oxidation protocol[34] terminal double bond present in compound **20** was converted to corresponding aldehyde **21**, which was subsequently subjected to Grignard reaction with vinyl magnesium bromide at −78 °C to furnish **22** in 87% yield. Allylic hydroxyl group present in **22** was protected as its TBS ether with TBDMSCl, imidazole to afford **9** in 92% yield.



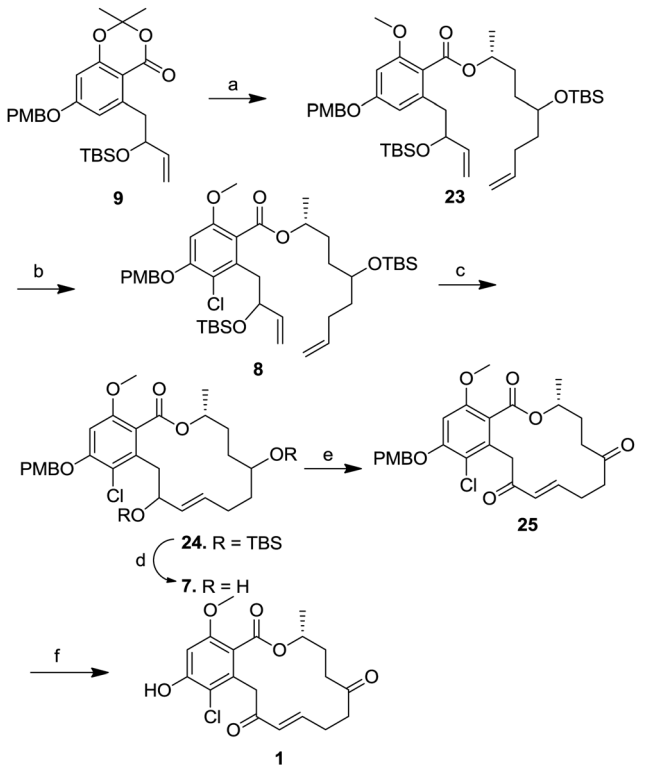
Scheme 2 *Reagents and conditions*: (a) $LiAlH_4$, THF, 0 °C–rt, 3 h, 85%; (b) PMBBr, NaH, 0 °C–rt, 8 h, 91%; (c) Raney Ni, Ethanol, 4 h, rt, 88%; (d) TEMPO, BAIB, CH_2Cl_2, 30 min, rt, 3-butenyl magnesium bromide, −78 °C–rt, 72% over two steps; (e) imidazole, TBSCl, CH_2Cl_2, 0 °C–rt, 4 h, 96%; (f) DDQ, CH_2Cl_2 : H_2O (9 : 1), 0 °C, 2 h, 89%.



Scheme 1 Retrosynthetic analysis of cryptosporiopsin A.



Scheme 3 *Reagents and conditions*: (a) acetone, TFA, TFAA, 0 °C–rt, 12 h, 55%; (b) PMBOH, DIAD, Ph_3P, CH_2Cl_2, 0 °C–rt, 4 h, 85%; (c) (1) Tf_2O, pyridine, 0 °C–rt, 10 h; (2) Bu_3Sn(allyl), LiCl, $Pd(PPh_3)_4$, DMF, 60 °C, 4 h, 76% over two steps; (d) OsO_4, $NaIO_4$, 2,6-lutidine, dioxane, H_2O, rt, 3 h, 89%; (e) vinylmagnesium bromide, THF, −78 °C, 4 h, 87%; (f) imidazole, TBDMSCl, 0 °C–rt, 3 h, 92%.



Scheme 4 *Reagents and conditions*: (a) (1) NaH, **10**, THF, 0 °C–rt, 5 h; (2) MeI, 0 °C–rt, 3 h, 85%; (b) NCS, chlorobenzene, 70 °C, 10 h, 77%, (c) Grubbs II, CH_2Cl_2, reflux, 18 h, 74%; (d) TBAF, THF, 0 °C–rt, 4 h, 95%; (e) DMP, CH_2Cl_2, 0 °C–rt, 5 h, 92%; (f) $TiCl_4$, 0 °C, 10 min, 87%.

After synthesizing fragments **9** and **10**, coupling of these two fragments was carried out by subjecting them to De Brabanders lactonization conditions led to the formation of compound **23** (≈1 : 1 : 1 : 1 diastereomeric mixture) in 85% yield.[35] Our next task was to introduce the chlorine functionality which was achieved by using *N*-chloro succinamide[36] in chlorobenzene to obtain compound **8** in 77% yield (Scheme 4). As it is a mixture of four compounds, the regioselectivity of chlorination at this stage was difficult to ascertain and we thought of confirming at the later stage of the synthesis. With the required diene compound in hand which sets the stage for crucial RCM reaction and the 14-membered macrolactone formation proceeded smoothly with Grubbs second generation catalyst under refluxing conditions to afford **24** (1 : 1 : 1 : 1 diastereomeric mixture) in 74% yield. At this stage the geometry of the double could not be confirmed because of the presence of two racemic centers. We proceeded further to remove the silyl groups which was achieved with 1 M solution of TBAF in THF at room temperature to give **7** (≈1 : 1 : 1 : 1 diastereomeric mixture) in 95% yield. Oxidation of secondary alcohols to ketones was achieved by Dess–Martin periodinane in CH_2Cl_2 to afford compound **25** in 92% yield as a single isomer. At this stage, *trans* geometry of the double bond was confirmed. Treatment of the compound **25** with titanium tetrachloride (10 equiv.) in CH_2Cl_2 at 0 °C furnished the target molecule **1** in 87% yield. After obtaining a good NMR spectrum, we confirmed the regioselectivity of chlorination reaction by taking the help of NOE experiment. The spectroscopic and analytical properties of **1** (^{1}H and ^{13}C NMR, and MS) were identical to those of reported for the natural product **1**. The optical rotation of synthetic **1** {$[\alpha]_D^{27}$ + 9.7 (*c* 1.05, MeOH)} was in good agreement with that of natural 1 {ref. 22 $[\alpha]_D^{20}$ + 11.0 (c 0.1, MeOH)}, which confirmed the absolute configuration.

Conclusions

In summary, the first total synthesis of cryptosporiopsin A (**1**) was accomplished in highly efficient way in 12 longest linear steps with 15.4% overall yield, starting from a known enantiomerically pure epoxide. The key steps of the synthesis were Jacobsen's hydrolytic kinetic resolution, Stille coupling, Grignard reaction, De Brabander's esterification and RCM reaction. This total synthesis has verified the absolute configuration of **1**. The strategy is both concise and flexible to produce additional analogues of **1** in enantiomerically pure form. Efforts to achieve this are currently underway in our laboratory.

Acknowledgements

We are thankful to the Director, CSIR-IICT and HoD, NPCD, for their kind support and encouragement. The authors thank CSIR, New Delhi for financial support as part of XII Five Year plan programme under title ORIGIN (CSC-0108). B.T. thanks the University Grant Commission (UGC), New Delhi, India for financial assistance in the form of fellowships.

Notes and references

1 (*a*) N. Winssinger and S. Barluenga, *Chem. Commun.*, 2007, 22; (*b*) T. Hofmann and H. H. Altmann, *C. R. Chim.*, 2008, **11**, 1318; (*c*) N. Winssinger, J. G. Fontaine and S. Barluenga, *Curr. Top. Med. Chem.*, 2009, **9**, 1419.
2 P. Delmotte and J. Delmotte-Plaquee, *Nature*, 1953, **171**, 344.
3 M. Stob, R. S. Baldwin, J. Tuite, F. N. Andrews and K. G. Gillette, *Nature*, 1962, **196**, 1318.
4 G. A. Ellestad, F. M. Lovell, N. A. Perkinson, R. T. Hargreaves and W. J. McGahren, *J. Org. Chem.*, 1978, **43**, 2339.
5 M. S. R. Nair and S. T. Carey, *Tetrahedron Lett.*, 1980, **21**, 2011.
6 R. J. Miksicek, *J. Steroid Biochem. Mol. Biol.*, 1994, **49**, 153.
7 W. T. Shier, *Rev. Med. Vet.*, 1998, **149**, 599.
8 (*a*) T. W. Schulte, S. Akinaga, S. Soga, W. Sullivan, B. Stensgard, D. Toft and L. M. Neckers, *Cell Stress Chaperones*, 1998, **3**, 100; (*b*) S. V. Sharma, T. Agatsuma and H. Nakano, *Oncogene*, 1998, **16**, 2639.
9 E. Moulin, V. Zoete, S. Barluenga, M. Karplus and N. Winssinger, *J. Am. Chem. Soc.*, 2005, **127**, 6999.
10 S. Barluenga, P.-Y. Dakas, Y. Ferandi, L. Meijer and N. Winssinger, *Angew. Chem.*, 2006, **118**, 4055.
11 (*a*) H. Tanaka, K. Nishida, K. Sugita and T. Yoshioka, *Cancer Sci.*, 1999, **90**, 1139; (*b*) A. Schirmer, J. Kennedy, S. Murli, R. Reid and D. V. Santi, *Proc. Natl. Acad. Sci. U. S. A.*, 2006, **103**, 4234.

12 J. Ninomiya-Tsuji, T. Kajino, K. Ono, T. Ohtomo, M. Matsumoto, M. Shiina, M. Mihara, M. Tsuchiya and K. Matsumoto, *J. Biol. Chem.*, 2003, **278**, 18485.

13 A. Zhao, S. H. Lee, M. Mojena, R. G. Jenkins, D. R. Patrick, H. E. Huber, M. A. Goetz, O. D. Hensens, D. L. Zink, D. Vilella, A. W. Dombrowski, R. B. Lingham and L. Huang, *J. Antibiot.*, 1999, **52**, 1086.

14 (*a*) W. A. Ayer, S. P. Lee, A. Tsuneda and Y. Hiratsuka, *Can. J. Microbiol.*, 1980, **26**, 766; (*b*) M. S. R. Nair and S. T. Carey, *Tetrahedron Lett.*, 1980, **21**, 2011.

15 V. Hellwig, A. Mayer-Bartschmid, H. Muller, G. Greif, G. Kleymann, W. Zitzmann, H.-T. Tichy and M. J. Stadler, *J. Nat. Prod.*, 2003, **66**, 829.

16 (*a*) M. Isaka, C. Suyarnsestakorn and M. Tanticharoen, *J. Org. Chem.*, 2002, **67**, 1561; (*b*) M. Isaka, A. Yangchum, S. Intamas, K. Kocharin, E. B. G. Jones, P. Kongsaeree and S. Prabpai, *Tetrahedron*, 2009, **65**, 4396.

17 S. Ayers, T. N. Graf, A. F. Adcock, D. J. Kroll, S. Matthew, E. J. Carcche de Blanco, Q. Shen, S. M. Swanson, M. C. Wani, C. J. Pearce and N. H. Oberlies, *J. Nat. Prod.*, 2011, **74**, 1126.

18 (*a*) H. Boettger-Tong, L. Murthy, C. Chiappetta, J. L. Kirkland, B. Goodwin, H. Adlercreutz, G. M. Stancel and S. Makela, *Environ. Health Perspect.*, 1998, **106**, 369; (*b*) B. S. Katzenellenbogen, J. A. Katzenellenbogen and D. Mordecai, *Endocrinology*, 1979, **105**, 33.

19 J. Dong, Y. Zhu, H. Song, R. Li, H. He, H. Liu, R. Huang, Y. Zhou, L. Wang, Y. Cao and K. Zhang, *J. Chem. Ecol.*, 2007, **33**, 1115.

20 (*a*) E. S. Abid, Z. Ouanes, W. Hassen, I. Baudrimont, E. Creppy and H. Bacha, *Toxicol. in Vitro*, 2004, **18**, 467; (*b*) A. Fürstner and K. Langemann, *J. Am. Chem. Soc.*, 1997, **119**, 9130; (*c*) H. J. Kwon, M. Yoshida, K. Abe, S. Horinouchi and T. Beppu, *Biosci., Biotechnol., Biochem.*, 1992, **56**, 538; (*d*) P. Chanmugam, L. Feng, S. Liou, B. C. Jang, M. Boudreau, G. Yu, J. H. Lee, H. J. Kwon, T. Beppu, M. Yoshida, Y. Xia, C. B. Wilson and D. Hwang, *J. Biol. Chem.*, 1995, **270**, 5418; (*e*) K. Takehara, S. Sato, T. Kobayashi and T. Maeda, *Biochem. Biophys. Res. Commun.*, 1999, **257**, 19; (*f*) N. A. Giese, and N. Lokker, *Int. Pat.* WO9613259.

21 (*a*) R. Hirschmann, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1278; (*b*) M. A. Koch and H. Waldmann, *Drug Discovery Today*, 2005, **10**, 471.

22 F. M. Talontsi, P. Facey, M. D. K. Tatong, M. T. Islam, H. Frauendorf, S. Draeger, A. V. Tiedemann and H. Laatsch, *Phytochemistry*, 2012, **83**, 87.

23 (*a*) A. Gradillas and J. Pérez-Castells, *Angew. Chem., Int. Ed.*, 2006, **45**, 6086; (*b*) A. Deiters and S. F. Martin, *Chem. Rev.*, 2004, **104**, 2199; (*c*) R. H. Grubbs, *Tetrahedron*, 2004, **60**, 7117; (*d*) J. Prunet, *Angew. Chem., Int. Ed.*, 2003, **42**, 2826; (*e*) J. A. Love, in *Handbook of Metathesis*, ed. R. H. Grubbs, Wiley-VCH, Weinheim, Germany, 2003, p. 296; (*f*) T. M. Trnka and R. H. Grubbs, *Acc. Chem. Res.*, 2001, **34**, 18; (*g*) A. Fürstner, *Angew. Chem., Int. Ed.*, 2000, **39**, 3012; (*h*) M. E. Maier, *Angew. Chem., Int. Ed.*, 2000, **39**, 2073; (*i*) R. H. Grubbs and S. Chang, *Tetrahedron*, 1998, **54**, 4413; (*j*) S. K. Armstrong, *J. Chem. Soc., Perkin Trans. 1*, 1998, 371; (*k*) K. Gerlach, M. Quitschalle and M. Kalesse, *Tetrahedron Lett.*, 1999, **40**, 3553; (*l*) M. Nevalainen and A. M. P. Koskinen, *Angew. Chem., Int. Ed.*, 2001, **40**, 4060.

24 (*a*) Y. Bharat, B. Thirupathi, G. Ranjit and D. K. Mohapatra, *Asian J. Org. Chem.*, 2013, **2**, 848; (*b*) B. Jena and D. K. Mohapatra, *Tetrahedron Lett.*, 2013, **54**, 3415; (*c*) B. Thirupathi, R. R. Gundapaneni and D. K. Mohapatra, *Synlett*, 2011, 2667; (*d*) D. K. Mohapatra, D. P. Reddy, U. Dash and J. S. Yadav, *Tetrahedron Lett.*, 2011, **52**, 151; (*e*) D. K. Mohapatra, R. Somaiah, M. M. Rao, F. Caijo, M. Mauduit and J. S. Yadav, *Synlett*, 2010, 1223; (*f*) D. K. Mohapatra, U. Dash, P. R. Naidu and J. S. Yadav, *Synlett*, 2009, 2129; (*g*) D. K. Mohapatra, G. Sahoo, D. K. Ramesh and G. N. Sastry, *Tetrahedron Lett.*, 2009, **50**, 5636; (*h*) D. K. Mohapatra, H. Rahman, R. Pal and M. K. Gurjar, *Synlett*, 2008, 1801; (*i*) D. K. Mohapatra, D. K. Ramesh, M. A. Giardello, M. S. Chorghade, M. K. Gurjar and R. H. Grubbs, *Tetrahedron Lett.*, 2007, **48**, 2621; (*j*) M. K. Gurjar, S. Karmakar and D. K. Mohapatra, *Tetrahedron Lett.*, 2004, **45**, 4525; (*k*) M. K. Gurjar, R. Nagaprasad, C. V. Ramana, S. Karmakar and D. K. Mohapatra, *ARKIVOC*, 2005, 237.

25 (*a*) L. P. C. Nielson, C. P. Stevenson, D. G. Blackmond and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2004, **26**, 1360; (*b*) S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 1307.

26 G. Sabitha, P. Padmaja, K. Sudhakar and J. S. Yadav, *Tetrahedron: Asymmetry*, 2009, **20**, 1330.

27 I. Paterson, R. A. Ward, P. Romea and R. D. Norcross, *J. Am. Chem. Soc.*, 1994, **116**, 3623.

28 A. D. Mico, R. Maragrita, L. Parlanti, A. Vescovi and G. Piancatelli, *J. Org. Chem.*, 1997, **62**, 6974.

29 Y. Oikawa, T. Yoshioka and O. Yonemitsu, *Tetrahedron Lett.*, 1982, **23**, 885.

30 R. G. Dushin and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1992, **114**, 655.

31 O. Mitsunobu, *Synthesis*, 1981, 1.

32 L. R. Subramanian, M. Hanack, L. W. K. Chang, M. A. Imhoff, P. Schleyer, F. Effenberger, W. Kurtz, P. J. Stang and T. E. Dueber, *J. Org. Chem.*, 1976, **41**, 4099.

33 (*a*) F.-T. Luo and R.-T. Wang, *Tetrahedron Lett.*, 1991, **32**, 7703; (*b*) S. Kamisuki, S. Takashi, Y. Mizushina, S. Anashima, K. Uramochi, S. Kobayashi, K. Sakaguchi, T. Nakata and F. Sugawara, *Tetrahedron*, 2004, **60**, 5695; (*c*) D. Martinez-Solorio, K. A. Belmore and M. P. Jennings, *J. Org. Chem.*, 2011, **76**, 3898; (*d*) J. S. Yadav, N. Thrimurthulu, Md. A. Rahman, J. S. Reddy, A. R. Prasad and B. V. Subbareddy, *Synlett*, 2010, 3657; (*e*) J. S. Yadav, S. Das, J. S. Reddy, N. Thrimurthulu and A. R. Prasad, *Tetrahedron Lett.*, 2010, **51**, 4050.

34 (*a*) W. Yu, Y. Mei, Z. Hua and Z. Jin, *Org. Lett.*, 2004, **6**, 3217; (*b*) T. K. Chakraborthy and A. K. Chattopadhyay, *J. Org. Chem.*, 2008, **73**, 3578; (*c*) T. N. Trotter, A. M. M. Alburry and M. P. Jennings, *J. Org. Chem.*, 2012, **77**, 7688.

35 A. Bhattacharjee, O. R. Sequil and J. K. De Brabander, *Tetrahedron Lett.*, 2000, **41**, 8069.

36 X. Leia and S. J. Danishefsky, *Adv. Synth. Catal.*, 2008, **350**, 1677.

